GRANULOCYTE MACROPHAGE COLONY STIMULATING FACTOR IMPROVES IMMUNOGENECITY OF HEPATITIS B VACCINE IN HEMODIALYSIS PATIENTS

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ABSTRACT

Only 20-50% of hemodialysis patients, develop protective antibodies following double dose Hepatitis B vaccination. Early reports suggest augmented response with concomitant use of Granulocyte macrophage colony stimulating factor (GMCSF). This study was done to assess the response rate to hepatitis B vaccine in hemodialysis patients with use of GMCSF. Seventeen patients were included in study, all received 40 mcg of hepatitis B vaccine at 0,1 and 2 months. Ten of these received 150 mcg of GMCSF with each dose of vaccine while 7 were taken as controls. Only one patient from control group (14.3%) while 5/10 (50%) patients from GMCSF group, developed protective antibodies, i.e. anti HBS titres > 10miu/ml ($p < 0.05$). Present study shows the beneficial effect of GMCSF when used as adjuvant with hepatitis B vaccine, in hemodialysis patients.

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KEY WORDS: GMCSF, Hepatitis B vaccine, Hemodialysis patients.

Introduction

Chronic renal failure patients are vulnerable to hepatitis B infection due to repeated blood transfusions, needle stick injuries and dialysis procedure. Prevalence of hepatitis B virus infection reported from dialysis centres is 1-30% [1,2]. This high risk population deserves protection against hepatitis B infection by vaccination. CDC has recommended double dose (40mcg) of the vaccine [3]. Some workers have documented that instead of three, four doses at 0,1,2, and 6 months produce higher antibody levels [4]. Despite conventional four double dose schedule only 30-50% of CRF patients develop protective antibodies (> 10miu/ml) and 50% of these patients lose these antibodies over 2-3 year period [5].

Various adjuvants have been tried to boost the response to vaccination e.g. interleukin-2 and lately granulocyte macrophage colony stimulating factor (GMCSF) [6-10]. This study was done to see the response of GMCSF as adjuvant to Hepatitis B vaccine in hemodialysis patients.

Material and Methods

Hepatitis B surface antigen negative dialysis dependent patients were the subjects of this study. Patients with malignancy, pregnancy or with positive viral markers were excluded from study. Patients with normal leucocyte count, platelet count and liver function tests were included in the study. Patients were divided in two arms, all patients in arm A and B received 40mcg hepatitis B

vaccine (Engerix-Smithkline Beecham) at 0,1 and 2 months. Patient in arm B, in addition received 150mcg of GMCSF (Leucomax-Novartis) on 0,1 and 2 months (on day of receiving Engerix). Erythropoietin was not administered within 48h of GMCSF. During the period of study none of the patients received immunoglobulins or steroids.

Hepatitis B antibody levels were estimated 30 days after the last dose and as per CDC criteria, antibody titres > 10 miu/ml (measured by ELISA) were taken as protective. The results were compared using Chi square test.

Results

Seventeen patients were included in the study, 7 in arm A and 10 patients in arm B. One of the 7 patients in arm A (14.3%) while 5/10 (50%) patients in arm B developed protective antibodies ($p < 0.05$). Data of these patients is reflected in Table 1.

TABLE 1

	Arm A (Hepatitis B vaccine)	Arm B (Hepatitis B vaccine + GMCSF)
Mean age	36.5 years (range 26-40)	38.1 years (range 30-78)
Sex (M/F)	6/1	8/2
Basic disease	CGN (4), CIN (3)*	CGN (6), CIN (3), ADPKD (1)*
Response	1/7 (14.3%)	5/10 (50%)

CGN : Chronic glomerulonephritis; CIN : Chronic interstitial nephritis; ADPKD : Autosomal dominant polycystic kidney disease

Discussion

Hepatitis B infection carries a bad prognosis, especially so in CRF patients since these patients due to

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immunocompromised state, are not able to clear the virus and become carriers. Conventionally, patients showing chronic hepatitis on liver biopsy are not accepted for transplantation. Immunosuppressive drugs used following transplantation increase antigenaemia resulting in rapid progression to cirrhosis. Liver related death is one of the foremost cause of mortality in such patients. Besides, these carriers are a source of infection to their spouses, other patients receiving dialysis and dialysis staff [1,2].

Hepatitis B vaccination is essential for prevention of this infection but despite double and more frequent administration only 30-50% patients develop protective antibodies [7-9]. Over 50% of those who develop these antibodies, lose them within 2-3 years necessitating frequent monitoring of antibody levels and booster vaccination [5]. It is obvious that those who develop protective antibodies develop them in low titres.

Repeated intradermal injections of the vaccine and use of interleukins are some of the approaches used to boost the antibody response. Macrophage dysfunction is also incriminated as the cause for poor response. GMCSF is one such modality and pilot studies using single and two doses of vaccine have shown beneficial response [7]. Malhotra et al in study of 15 patients, using two doses of GMCSF found a response rate of 66.6% [8]. Sudhagar et al using 20 mcg of hepatitis vaccine and single dose of GMCSF found a surprisingly high response rate of 87.5% among their 8 patients [9]. In another study 11 out of 12 non responders to hepatitis B vaccine seroconverted with single dose of 300 µg of GMCSF [10]. We used the adjuvant with each dose of vaccine (three doses) and found the response rate of 50%. How the GMCSF acts is not clear but possible mechanisms are [7-9] :

1. Immune stimulation
2. Maturation of dendritic cells
3. Activation of antigen presenting cells

For production of antibodies every antigenic stimulus needs to reach the antibody producing cells (B and T helper cells). In chronic renal failure patients, macrophage probably plays an important role in stimulating the antigen-presenting cell. GMCSF by stimulating the macrophage helps the antigenic stimu-

lus to reach the target site thereby enhancing the antibody production.

How many doses and what dose should be used is not yet clear but logical approach of repeated doses along with the vaccination appears sound. Why some patients develop protective antibodies while others do not, probably is related to the immune status of the patients. Further randomised controlled trials with larger number of patients to assess the dose response, as per the immune status are required to give definitive guidelines.

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